Hyperlipidemia: Case Studies as Evidence for Optimal Treatment

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Objectives

- Summarize the key evidence from recent large lipid treatment trials.
- Explain and apply the NCEP/ATP III guidelines to patients.
- Discuss the risks and benefits of various treatment options and the evidence supporting these options for use in patients.
- Have fun with real cases!!

Why Bother?

- Optimum treatment of lipids helps in the primary & secondary prevention of ASCVD; still our nation's #1 killer
- We have a long way to go…
  - RAND; 1st National Report Card on Quality of Care; NEJM 26 June 2003
  - Only 48.6% of patients are receiving recommended care for hyperlipidemia

Pre-2000

- Statin Trials: huge, prospective, double-blind, placebo controlled.
- Two Types: Primary Prevention
  Secondary Prevention

Both types proved that statins (simvastatin, pravastatin, lovastatin) could dramatically reduce morbidity & mortality from ASCVD and all-cause mortality.

NCEP/ATP III – 15 May 2001

- **www.nhlbi.nih.gov**
- **LDL remained the main treatment goal, but LDL goals lowered**
- **Raised acceptable HDL to 40**
- **Lowered TG goal to 150**
- **Risk Factor assessment enhanced with the 10-yr Framingham risk calculator**
- **Added the Metabolic Syndrome to Tx**

NCEP/ATP III – 9 Steps

- Step 1: Obtain, complete & fasting lipids.
- Interpret: LDL < 100 optimal
  LDL 100-129 near optimal
  LDL 130-159 borderline high
  LDL 160-189 high
  LDL >190 very high

NCEP/ATP III

- Step 2: Identify if patient has CAD or equivalent (PAD, DM, AAA, Carotid)
- Step 3: Risk factor assessment (HTN, FHx, Tob, Age & Sex, HDL<40 or >60)
- Step 4: If 2 or more risk factors; do Framingham 10-yr risk assessment.

NCEP/ATP III – Step 5

Risk Category	**LDL Goal**	**Start T.L.C.**	**Start Drug Treatment**
CHD/10yr risk>20%	<100mg/dl	>100mg/dl	>100 – 129mg/dl
2+RF or 10yr<20%	<130mg/dl	>130mg/dl	>130 – 160mg/dl
0-1 risk	<160mg/	>160mg/	>160

NCEP/ATP III – Step 6

- Initiate Therapeutic Lifestyle Changes (TLC)
  - AHA Step 2 diet
  - Soluble fiber 10-25gm/day
  - Plant sterols/Sitostanol (Benecol®, Take Control® margarines) - lower LDL 10%
  - Increased exercise
  - Weight management

NCEP/ATP III – Step 7

- Add drug therapy simultaneously to TLC in patients with CHD or equivalent. Add drugs after 3 months if TLC not effective in other risk categories.

- Best unbiased source for review of drug treatment: “The Medical Letter: Choice of lipid regulating drugs” 43:2001,pp43-48. 2003 update

Drugs – Step 7 (cont.)

- **Resins**- (cholestyramine,colestid, colesevelam): lower LDL; adjunct to statins; GI side effects/malabsorption issues
- **Niacin-** “miracle agent”, cheap & moves every parameter in the right direction. But, side effects problematic. Need slow dose titration and pre-med with ASA. Caution with Diabetes; can worsen glycemic control

  Most potent increase of HDL.

Drugs – Step 7 (cont)

- **Fibrates** – (fenofibrate, gemfibrozil) lower TG and raise HDL. Can combine with statins but caution re: hepatic side effects. Cutting statin dose by ½ is good rule.
- Keep simvastatin dose no greater than 10mg if combined with a fibrate or >1000mg of niacin.

Newer Drugs – Step 7 (cont.)

- **Ezetimibe (Zetia®)-** new class that inhibits the intestinal absorption of cholesterol. Lowers LDL 17%, TG 6%, increases HDL by 1.3%. Combined with a statin increases effects of statin by 10-15% w/o side effects. VERY well tolerated at 10mg/d. Does increase cholesterol in bile; ?cholelithiasis.

  May render resins obsolete….

Newer Drugs – Step 7 (cont)

- **<u>Lovastatin + Niacin (Advicor®)-</u>** in fixed combos 20/500, 20/750, 20/1000. Increase dose *monthly* up to max 40/2000. Max dose w/ LDL decrease 45%, TG 42%, and HDL increase by 41%. Causes less flushing and hepatic effects than any niacin formulation. Greater risk of myopathy than a statin alone.

Drugs – Step 7 (cont.)

- **<u>Statins-</u>** All w/ anti-inflammatory effects. None safe in pregnancy. All are more potent by 10-15% with evening dosing.

  - muscle pain = 1-5%

  - hepatitis (transaminases>3x nl.) = 0.5%

  - rhabdomyolysis = rare; incidence *rates per million Rx's*: pravastatin0.04, lovastatin0.19 atorvastatin 0.04, simvastatin 0.12.

  (*cerivistatin was 16-80x these rates!!)*

So Are Statin's safe?

- 3 Meta-analyses: Muldoon et al. BMJ 2001:322:11-15. Cholesterol reduction and non-illness mortality: meta-analysis of randomized clinical trials.
- "Trials using statins did not show a rise in non-illness mortality, whereas a trend towards increased deaths from suicides and violence was observed in trials of dietary intervention and non-statin drugs"

Statin Safety

- Do statins cause cataracts? Schlienger et al. Arch Int Med 2001 Sep 10;161(16):2021-26 “Risk of cataract in patients treated with statins”

answer: **NO**

Statin Safety

- Do statins cause cancer? Bjerre et al. Amer J Med 2001 :110(9):716-23. “Do statins cause cancer? A meta-analysis of large randomized clinical trials”.
- No association between statin use and the risk of fatal and non-fatal cancers.

Drugs – Step 7 (cont.)

- Atorvastatin – greatest LDL lowering w/ good TG lowering
- Lovastatin: take w/ food; generic version
- Pravastatin: least drug interactions due to different elimination pathway; take on empty stomach
- Simvastatin: #2 in potency; lots of data
- Fluvastatin: less potent; poor prevention data
- Rosuvastatin: new release; very potent; 5 - 40 mg (CRESTOR®); may raise HDL a bit more & lower TG. Caution w/ CrCl<30cc/min and ??? in Asians.

Statin Pearls

- Elevated transaminases on statins; (unless reaching 3x normal), are not a reason to stop the statin – they are are a reason to watch closely.
- Statin side effects are often agent specific, not always class specific.
- Unexplained myalgias may occur on statins without CK elevation. Try a different statin.

Statin Pearls

- Rhabdomyolysis is uncommon unless CK is elevated to 10 x normal.
- Unless you enjoy driving yourself nuts; do not check CK serially in patients on statins. Remember vigorous yard work will bump your CK!
- Use the minimum dose of statin required to reach goal to lessen side effects. But – what about the PROVE-IT study? (NEJM 8 April 2004)

PROVE-IT Trial

- Designed to “PROVE” that 80mg atorvastatin was no better than 40 mg pravastatin in secondary prevention.
- But, atorvastatin was superior *as early as 30 days of therapy*. In just 24 mths the atorvastatin group (meanLDL=62) had 16% less of all CV events. 28% less mortality than pravastatin group (meanLDL=95)

PROVE-IT Trial

- WOW!
- Evidence from mammalian species had shown that atherogenesis stops & reverses at an LDL <80 – now some clinical outcome data.
- TNT & IDEAL are primary prevention trials EDC 2004/2005 looking at how low should you go
- “There will soon be a sea change in the prevention & management of ASCVD” – Eric Topol, MD

NCEP/ATP III – Step 8

- Identify Metabolic Syndrome: (3 of 5)
  - SBP>130, FBS>110, TG>150, HDL<40 in men and <50 in women, waist>40”men, 35”women

Aggressively:

- Treat underlying causes of overweight and physical inactivity.
- Treat HTN, use ASA for CHD patients

NCEP/ATP III – Step 9

- Treat elevated TG (>150mg/dl)
  - First lower LDL; if TG still >200 consider adding/increasing drug therapy
  - But, if TG >500mg/dl, first lower triglycerides to prevent pancreatitis. When they are <500 then return to LDL lowering
  - Treat HDL <40 after lowering LDL.

CASES

- All real cases. No “perfect answers”.
- All present real Family Practice dilemmas.
- Will use the evidence to help formulate a “best” answer.
- Use cases t g edge info.

Case #1- The Well Elderly

- 82 yr old woman with no significant medical history who checked her cholesterol at a health fair and was told she needed to see her family doctor because it was high.
- Your recheck:
- TC=254 LDL=188 HDL=41 TG=125

Case #1

- PMHx: osteoarthritis and systolic HTN
- Meds: celecoxib 100mg qd, HCTZ 25mg qd
- FHx: 3 relatives who have lived to >100yrs
- PE: 66” 138lbs P=70 BP=158/77
  - Rest of exam non-contributory

  - WHAT DO YOU DO?

Case #1

- Apply NCEP: risk assessment? 2 RF so Framingham Risk = 27% 10yr risk
- Check Step 5?

- If we choose a med, best med to lower her LDL is a statin.
- But, should we prescribe a med?

Case # 1

- Things to consider:
- Statin trials excluded folks >65 yrs
- But, NNT at this age is 4:1 vs. 35:1 for a middle aged man.
- Side effects? Drug interactions? Cost?
- PROSPER

Case # 1

- PROSPER; Lancet 2002:360; pp1623-30.
- Used 40mg/d of pravastatin in patients 70-82 yrs of age (majority women) in both primary **and** secondary prevention.
- 24% Rel Risk Red (RRR) of CHD death, 25% RRR in TIA, in just 3 years of use.
- Drugs tolerated extremely well-even w/ multi-Rx.
- “Long-term statin therapy should be considered routinely largely irrespective of age”

Case # 1

- Maycock CA et al; JACC 2002;40:1777-85.
- Statin tx in patients >80yrs. Mortality rate was **8.5%** in those on statins **vs. 29.5%** in those not taking statins.

- So you could consider an RX Statin for this elderly woman; certainly need to optimize her HTN control as first priority.

Case # 2 – The Young

- 23 yr old medical student who presents with a CC of : “I want to do something to prevent me from getting a heart attack”
- PMHx: SAR uses Flonase®
- FHx: MI in F at 43; 2 Uncles at 37, 39 yrs; PGF died “suddenly at a BBQ” at 40.
- PE: 70” 170lbs P=54 BP=126/72
- TC = 243 HDL = 34 TG = 120 LDL = 185

Case #2 – The Young

- Risk Assessment: 2 RF (HDL + FHx) so Framingham = 1% 10 yr risk
- Begin TLC; what about drug Tx?
- BUT; these guidelines are for those>35yrs?
- Also; trials have excluded patients this young…

Case #2 – The Young

- What do we know?
- Military autopsy studies and the ongoing PDAY study (from New Orleans) shows that atherogenesis starts as young as 2yrs of age with the development of fatty streaks. Tremendous correlation between anatomic ASCVD and serum markers as well as FHx across all ages.

Case #2 – The Young

- NCEP/ATP III – gives guidance for younger adults (men 20-35 & women 20-45) It recognizes that; “even though clinical CHD is relatively rare in young adults, coronary atherosclerosis may progress rapidly … and elevated cholesterol in young adulthood predicts a higher rate of premature CHD in middle age.” Says that young men who smoke or who have LDL>160 may be candidates for lipid lowering drugs.

Case #2 – The Young

- Consider using a statin if LDL remains >160 despite ***aggressive*** TLC.
- Recognize that the NNT will be high (40-60:1).
- Recognize that prospective trial data is lacking.
- Recognize that doing nothing is probably not a reasonable choice…

Case #3 – Diabetes

- 55 year old male with Type II Diabetes and HTN for 5 years. He has refused treatment for elevated cholesterol in the past – but is willing to discuss it now.
- Other PMHx: GERD, Irritable Bowel
- Meds: Metformin, lisinopril, omeprazole, metamucil
- FHx: DM, MI in F at 58, PGF at 60

Case #3 - Diabetes

- TSH: normal
- TC = 235 HDL = 28 TG = 185 LDL =170
- PE: 69” 268lbs P=74 BP = 136/82
- An obese male who seems to be mildly short of breath just moving around the exam room.

Case #3 - Diabetes

- Risk Assessment: EASY ! DM=CHD
- Want LDL < 100.
- Begin TLC; also consider the simultaneous start of ASA and a statin.
- Evidence: MRC/BHF Heart protection study of cholesterol lowering in 20,536 high risk individuals. Lancet. 2002; 360: 7-22.

Case #3 - Diabetes

- This large study showed that treatment with simvastatin; *regardless of its numerical effect on lipid values* helped to reduce all endpoints (MI, CVA, revascularization). This was especially true for those with Diabetes.

Case #3 - Diabetes

- Start simvastatin 20 mg po qd and check LFT at 6weeks. (normal) Check LFT and lipids at 12 weeks. LFT nl but;
- TC = 198 HDL = 30 TG = 180 LDL = 132
- You increase simvastatin to 40 mg and recheck in 12 weeks;
- TC = 178 HDL = 31 TG = 174 LDL = 112

Case # 3 - Diabetes

- What next?
- Optimize your Diabetes control
- Optimize your dietary and exercise plan
- Consider adding a fibrate
- Consider a change to Advicor®
- Don’t ignore the low HDL/high TG – see Step 8/9 of the NCEP/ATP III

Case # 4 – “Middle-of the Road”

- 45 year old woman who on a routine lipid screen has the following values:
- TC = 203 HDL=48 TG = 155 LDL = 124
- PMHx: negative, smoker
- Meds: daily vitamin
- FHx: MI in F age 60, M age 64
- PE: 55” 130lbs P=72 BP=118/68

Case #4 – “Middle of the Road”

- Risk Factors: 2 ; Framingham = 5% risk
- NCEP/ATP III says that she is at her LDL goal; e.g. <130
- But, concerns remain: FHx, Smoking, HDL is <50 & TG >150; both less than ideal.
- What do you do with this “middle-of-the-road” risk profile?

Case# 4 – Middle of the Road

- Consider a new idea: measure her hs-CRP
- Facts: CRP is a marker of inflammation.
- ASCVD is a disease of inflammation
- Multiple prospective epidemiological (vs. interventional studies) have shown that CRP can predict MI,CVA, PAD, sudden cardiac death.

Case #4 – Middle of the Road

- Hs-CRP assays are now widely available; can check non-fasting, anytime of day.
- < 1mg/l = low risk
- 1-3mg/l = moderate risk
- >3mg/l = high risk
- **>10mg/l = invalid for cardiac risk prediction;consider 1° inflammatory disease, trauma, serious infection.**

Case # 4 – Middle of the Road

- CRP predicts risk *independently* of age, smoking, LDL, HDL, BP, Diabetes, sex.
- CRP has long-term predictive value
- CRP is a stronger predictor of risk than LDL
- CRP does not supplant other risk factor assessment – it is a powerful adjunct!

Case # 4 – Middle of the Road

- CRP is a stronger predictor of risk than magnetic resonance based evaluation of LDL particle size and concentration. (It is also much less expensive..)
- BUT: no definitive evidence yet that lowering CRP will reduce ASCVD event rates vs. for reducing BP, or LDL cholesterol.

Case #4 – Middle of the Road

- PRINCE (PRavastatin INflammation/Crp Evaluation trial; JAMA 2001:286;64-70. And other trials have proven that Statins lower CRP 15-25% within 6 weeks of initiation.
- Weight loss, exercise and smoking cessation also lower CRP.

Case # 4 – Middle of the Road

- Ridker et al. NEJM Measurement of CRP for the targeting of statin therapy in the primary prevention of acute coronary events. 2002;344: pp1959-1965.
- JFP POEM (March 2003): “CRP is an independent predictor of a first CV event in women and appears to be a stronger predictor than LDL cholesterol levels”.

Case # 4 – Middle of the Road

- ***Most conservative view:***
- JAMA Aug 20, 2003 290:7; p932-940.
- 3 situations to use hs-CRP
  - 1.) asymptomatic; strong FHx, no other RF's
  - 2.) pts. w/ premature ASCVD and no explanation
  - 3.) pts. w/ recurrent events despite optimal control of all conventional RF's

Case # 4 – Middle of the Road

- CARE & AFCAPS/TEXCAPS both suggest that the benefit of statin therapy among those with *low LDL but high CRP may be as large as those with overt hyperlipidemia.*
- How to answer this ?
- 2003: 15,000 patients with native LDL<130 but CRP above 2.0mg/l. All will be put on a statin for prevention. What will happen?

Case # 4 – Middle of the Road

- What does this mean for our patient?
- CRP is most useful in those judged at intermediate risk and in primary prevention.
- Review; 45 yr old woman with an LDL<130 but +FHX and other borderline risks…eg a 5% Framingham risk
- HOW about checking an hs-CRP to further assess her risk ?

Case # 4 – Middle of the Road

- CRP = 3.2mg/l HIGH risk
- Studies have proven she is in fact at risk; more than her LDL would tell us. What to do?
- Smoking cessation will lower CRP
- Statins will lower her CRP
- But, no prospective proof that this will change her outcome. It is your call, Doctor!

Case # 5 – The Unreachable Goal

- 60 yr old male returns to see you 3 months after a 4vCABG. He feels great. At his last visit with his CT surgeon he was told; “follow-up with your family doctor to get your cholesterol in control”
- PMHX: HTN x 20 yrs, BPH, ED, mild OA
- MEDS: ASA, Metoprolol 50 mg po bid, Viagra®,

  Simvastatin 20 mg po qd
- FHX: F with CVA at 68

Case # 5 – The Unreachable Goal

- PE: 70” 160lbs P=60 BP=124/76
- Cor: RRR, no m/r/g, no jvd, healed median sternotomy scar
- Ext: no edema
  Lungs: slight dec. breath sounds
- TC=180, HDL=42 TG=100 LDL=118

Case # 5 – The Unreachable Goal

- Risk Assessment = he has CHD; 2° prev.
- Goal LDL is <100 per NCEP
- At this level atherogenesis seems to arrest
- At an LDL of 80 in mammalian species atherogenesis reverses. Also the PROVE-IT trial shows that an LDL of 62 was superior to an LDL of 95.

Case #5 – The Unreachable Goal

- You decide to increase the simvastatin to 40mg po qd.
- 6 weeks later; TC= 170 TG=105 HDL=42 LDL=107
- What do you do?

Case # 5 – The Unreachable Goal

- Many options: 1)increase simvastatin to 80 mg or change to atorvastatin or rosuvastatin.
- PROBLEM: inc risk of side effects and less LDL lowering effect as you inc statin doses. For every doubling of dose, LDL decreases by only 6 %. A threefold higher dose by 12% and a fourfold increase lowers LDL cholesterol by only 18%.

Case # 5 – The Unreachable Goal

- 2.) Add Ezetimibe 10 mg po qd: less chance of side effects; should help to reach goal LDL easily.
- 3.) Intensify diet; Ornish Plan; add soluble fiber, add soy, add omega-3 fatty acids.
- 4.) Be satisfied and await more trials…

Summary

- **7 Points to make you**
- 1) Primary & Seconda
  Prevention of ASCVD a
  possible!
  2) NCEP/ATP III at

www.nhlbi.nih.gov is a wonderful tool.

Summary – 7 Points

- 3) Better medication options are a help: Ezetimibe, Advicor®, new statins and a cleaner understanding of statin side effects
- 4)Attack the metabolic syndrome!! A multi-modal treatment plan is best.
- 5) Don’t ignore a chance for prevention because your patient is >70 or <35.

Summary – 7 Points

- 6) hs-CRP is a powerful new tool to predict risk; especially in those at intermediate risk.

  But, we need prospective proof that lowering it will help reduce ASCVD endpoints.

  7) Try to get to goal; How low should we go? Await the TNT and IDEAL trials & anticipate new ATP-IV guidelines.

Thanks for your Attention!